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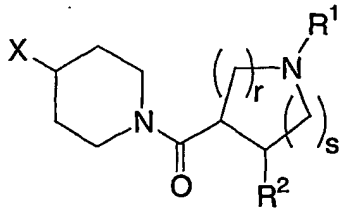
(54) Title: ACYLATED PIPERIDINE DERIVATIVES AS MELANOCORTIN-4 RECEPTOR AGONISTS

(57) Abstract: Certain novel 4-substituted N-acylated piperidine derivatives are agonists of the human melanocortin receptor(s) and, in particular, are selective agonists of the human melanocortin-4 receptor (MC-4R). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of MC-4R, such as obesity, diabetes, sexual dysfunction, including erectile dysfunction and female sexual dysfunction.

WHAT IS CLAIMED IS:

1. A compound of structural formula I:



(I)

or a pharmaceutically acceptable salt thereof;

wherein

r is 1 or 2;

s is 0, 1, or 2;

n is 0, 1 or 2;

p is 0, 1, or 2;

R^1 is selected from the group consisting of

hydrogen,

amidino,

C_{1-4} alkyliminoyl,

C_{1-10} alkyl,

$(CH_2)_n$-C_{3-7} cycloalkyl,

$(CH_2)_n$-phenyl,

$(CH_2)_n$-naphthyl, and

$(CH_2)_n$-heteroaryl wherein heteroaryl is selected from the group consisting of

(1) pyridinyl,

(2) furyl,

(3) thienyl,

(4) pyrrolyl,

(5) oxazolyl,

(6) thiazolyl,

(7) imidazolyl,

(8) pyrazolyl,

(9) isoxazolyl,
(10) isothiazolyl,
(11) pyrimidinyl,
(12) pyrazinyl,
(13) pyridazinyl,
(14) quinolyl,
(15) isoquinolyl,
(16) benzimidazolyl,
(17) benzofuryl,
(18) benzothienyl,
(19) indolyl,
(20) benzthiazolyl, and
(21) benzoxazolyl;

in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo;

R^2 is selected from the group consisting of
phenyl,
naphthyl, and
heteroaryl wherein heteroaryl is selected from the group consisting of
(1) pyridinyl,
(2) furyl,
(3) thienyl,
(4) pyrrolyl,
(5) oxazolyl,
(6) thiazolyl,
(7) imidazolyl,
(8) pyrazolyl,
(9) isoxazolyl,
(10) isothiazolyl,
(11) pyrimidinyl,
(12) pyrazinyl,
(13) pyridazinyl,

(14) quinolyl,
(15) isoquinolyl,
(16) benzimidazolyl,
(17) benzofuryl,
(18) benzothienyl,
(19) indolyl,
(20) benzthiazolyl, and
(21) benzoxazolyl;

in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3;

each R^3 is independently selected from the group consisting of
C_{1-6} alkyl,
$(CH_2)_n$-phenyl,
$(CH_2)_n$-naphthyl,
$(CH_2)_n$-heteroaryl,
$(CH_2)_n$-heterocyclyl,
$(CH_2)_nC_{3-7}$ cycloalkyl,
halogen,
OR^4,
$(CH_2)_nN(R^4)_2$,
$(CH_2)_nC{\equiv}N$,
$(CH_2)_nCO_2R^4$,
NO_2,
$(CH_2)_nNR^4SO_2R^4$
$(CH_2)_nSO_2N(R^4)_2$,
$(CH_2)_nS(O)_pR^4$,
$(CH_2)_nNR^4C(O)N(R^4)_2$,
$(CH_2)_nC(O)N(R^4)_2$,
$(CH_2)_nNR^4C(O)R^4$,
$(CH_2)_nNR^4CO_2R^4$,
$(CH_2)_nNR^4C(O)$-heteroaryl,
$(CH_2)_nC(O)NR^4N(R^4)_2$,
$(CH_2)_nC(O)NR^4NR^4C(O)R^4$,
$O(CH_2)_nC(O)N(R^4)_2$,

CF_3,
CH_2CF_3,
OCF_3, and
OCH_2CF_3;

in which heteroaryl is as defined above; phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy; and wherein any methylene (CH_2) carbon atom in R^3 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl; or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R^4 is independently selected from the group consisting of
hydrogen,
C_{1-6} alkyl,
$(CH_2)_n$-phenyl,
$(CH_2)_n$-heteroaryl,
$(CH_2)_n$-naphthyl,
$(CH_2)_n$-heterocyclyl,
$(CH_2)_nC_{3-7}$ cycloalkyl, and
$(CH_2)_nC_{3-7}$ bicycloalkyl;

wherein alkyl, phenyl, heteroaryl, heterocyclyl, and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy; or two R^4 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC_{1-4} alkyl;

each R^5 is independently selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
$(CH_2)_n$-phenyl,
$(CH_2)_n$-naphthyl,
$(CH_2)_n$-heteroaryl, and
$(CH_2)_nC_{3-7}$ cycloalkyl;

wherein heteroaryl is as defined above; phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3; alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo; and wherein any methylene (CH_2) in R^5 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl; or two R^5 groups together with the atom to which they are attached form a 5- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC_{1-4} alkyl; and

X is selected from the group consisting of
C_{1-8} alkyl,
$(CH_2)_nC_{3-8}$ cycloalkyl,
$(CH_2)_n$-phenyl,
$(CH_2)_n$-naphthyl,
$(CH_2)_n$-heteroaryl,
$(CH_2)_n$heterocyclyl,
$(CH_2)_nC{\equiv}N$,
$(CH_2)_nCON(R^5R^5)$,
$(CH_2)_nCO_2R^5$,
$(CH_2)_nCOR^5$,
$(CH_2)_nNR^5C(O)R^5$,
$(CH_2)_nNR^5CO_2R^5$,
$(CH_2)_nNR^5C(O)N(R^5)_2$,
$(CH_2)_nNR^5SO_2R^5$,
$(CH_2)_nS(O)_pR^5$,
$(CH_2)_nSO_2N(R^5)(R^5)$,
$(CH_2)_nOR^5$,
$(CH_2)_nOC(O)R^5$,
$(CH_2)_nOC(O)OR^5$,
$(CH_2)_nOC(O)N(R^5)_2$,
$(CH_2)_nN(R^5)(R^5)$, and
$(CH_2)_nNR^5SO_2N(R^5)(R^5)$;

wherein heteroaryl is as defined above; phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3; alkyl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three

groups independently selected from R^3 and oxo; and wherein any methylene (CH_2) in X is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl;

2. The compound of Claim 1 wherein R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, $(CH_2)_{0-1}C_{3-6}$ cycloalkyl, and $(CH_2)_{0-1}$-phenyl; wherein phenyl is unsubstituted or substituted with one to three groups independently selected from R^3; and alkyl and cycloalkyl are optionally substituted with one to three groups independently selected from R^3 and oxo.

3. The compound of Claim 1 wherein R^2 is phenyl or thienyl optionally substituted with one to three groups independently selected from R^3.

4. The compound of Claim 3 wherein R^2 is phenyl optionally substituted with one to three groups independently selected from R^3.

5. The compound of Claim 1 wherein X is selected from the group consisting of

$(CH_2)_n$-phenyl,
$(CH_2)_n$-naphthyl,
$(CH_2)_n$-heteroaryl,
$(CH_2)_nC_{3-8}$ cycloalkyl, and
$(CH_2)_n$-heterocyclyl;

wherein phenyl, naphthyl, and heteroaryl are optionally substituted with one to three groups independently selected from R^3; cycloalkyl and heterocyclyl are optionally substituted with one to three groups independently selected from R^3 and oxo; and wherein any methylene (CH_2) group in X is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl.

6. The compound of Claim 5 wherein X is selected from the group consisting of

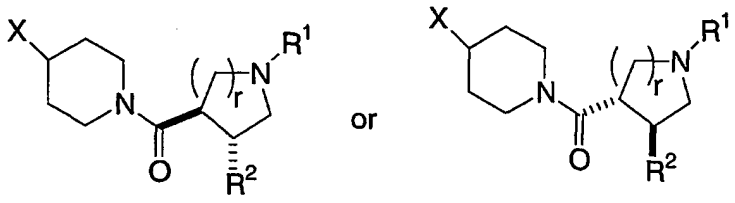
$(CH_2)_{0-1}$-phenyl,
$(CH_2)_{0-1}$-heteroaryl, and
$(CH_2)_{0-1}$-heterocyclyl;

wherein phenyl and heteroaryl are optionally substituted with one to three groups independently selected from R^3; heterocyclyl are optionally substituted with one to three groups independently selected from R^3 and oxo; and CH_2 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl.

7. The compound of Claim 6 wherein X is phenyl optionally substituted with one to three groups independently selected from R^3.

8. The compound of Claim 1 wherein r is 1 or 2 and s is 1.

9. The compound of Claim 1 of structural formula IIa or IIb of the indicated *trans* relative stereochemical configuration:



(IIa) or (IIb)

or a pharmaceutically acceptable salt thereof;

wherein

r is 1 or 2;

n is 0, 1, or 2;

p is 0, 1, or 2;

R^1 is hydrogen, amidino, C_{1-4} alkyliminoyl, C_{1-6} alkyl, C_{5-6} cycloalkyl, $(CH_2)_{0-1}$ phenyl, or $(CH_2)_{0-1}$ heteroaryl; wherein phenyl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo;

R^2 is phenyl or thienyl optionally substituted with one to three groups independently selected from R^3;

each R^3 is independently selected from the group consisting of

C_{1-6} alkyl,
$(CH_2)_n$-heteroaryl,
$(CH_2)_n$-heterocyclyl,
halogen,
OR^4,
$(CH_2)_nN(R^4)_2$,
$(CH_2)_nC{\equiv}N$,
$(CH_2)_nCO_2R^4$,
$(CH_2)_nNR^4SO_2R^4$
$(CH_2)_nSO_2N(R^4)_2$,
$(CH_2)_nS(O)_pR^4$,
$(CH_2)_nNR^4C(O)N(R^4)_2$,
$(CH_2)_nC(O)N(R^4)_2$,
$(CH_2)_nNR^4C(O)R^4$,
$(CH_2)_nNR^4CO_2R^4$,
$(CH_2)_nNR^4C(O)$-heteroaryl,
$(CH_2)_nC(O)NR^4N(R^4)_2$,
$(CH_2)_nC(O)NR^4NR^4C(O)R^4$,
$O(CH_2)_nC(O)N(R^4)_2$,
CF_3,
CH_2CF_3,
OCF_3, and
OCH_2CF_3;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy; and wherein any methylene (CH_2) carbon atom in R^3 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl; or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R^4 is independently selected from the group consisting of

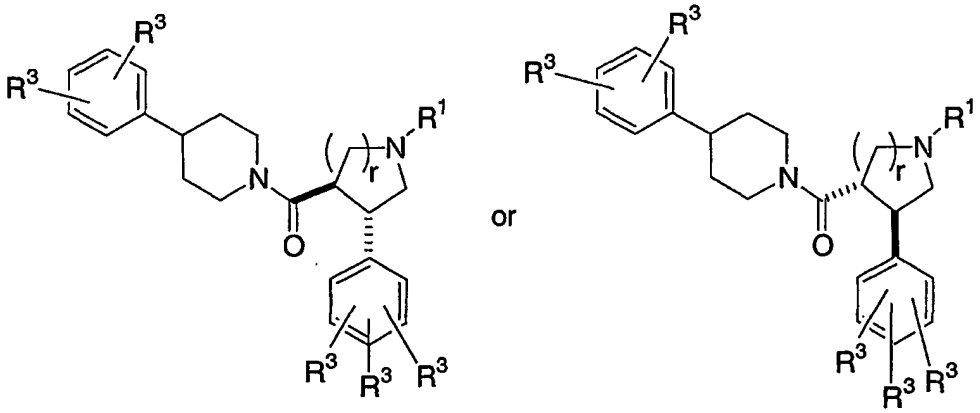
hydrogen,
C_{1-8} alkyl,
phenyl,
heteroaryl,
$(CH_2)_{0-1}$ heterocyclyl, and
C_{3-6} cycloalkyl;

wherein alkyl, phenyl, hetroaryl, heterocyclyl, and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy;

or two R^4 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC_{1-4} alkyl; and

X is phenyl or heteroaryl each of which is optionally substituted with one to three groups independently selected from R^3.

10. The compound of Claim 1 of structural formula IIIa or IIIb of the indicated *trans* relative stereochemical configuration:



(IIIa) (IIIb)

or a pharmaceutically acceptable salt thereof;

wherein

r is 1 or 2;

R^1 is hydrogen, C_{1-4} alkyl, or $(CH_2)_{0-1}$ phenyl;

each R^3 is independently selected from the group consisting of

C_{1-6} alkyl,

$(CH_2)_{0-1}$-heteroaryl,

$(CH_2)_{0-1}$-heterocyclyl,

halogen,

OR^4,

$(CH_2)_{0-1}N(R^4)_2$,

$(CH_2)_{0-1}C{\equiv}N$,

$(CH_2)_{0-1}CO_2R^4$,

$(CH_2)_{0-1}NR^4SO_2R^4$

$(CH_2)_{0-1}SO_2N(R^4)_2$,

$(CH_2)_{0-1}S(O)_pR^4$,

$(CH_2)_{0-1}NR^4C(O)N(R^4)_2$,

$(CH_2)_{0-1}C(O)N(R^4)_2$,

$(CH_2)_{0-1}NR^4C(O)R^4$,

$(CH_2)_{0-1}NR^4CO_2R^4$,

$(CH_2)_{0-1}NR^4C(O)$-heteroaryl,

$(CH_2)_{0-1}C(O)NR^4N(R^4)_2$,

$(CH_2)_{0-1}C(O)NR^4NR^4C(O)R^4$,

$O(CH_2)_{0-1}C(O)N(R^4)_2$,

CF_3,

CH_2CF_3,

OCF_3, and

OCH_2CF_3;

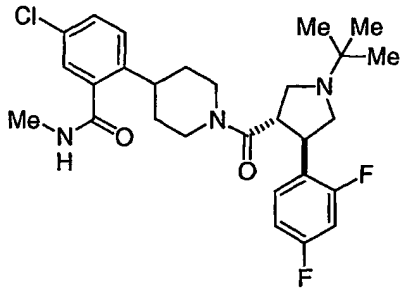
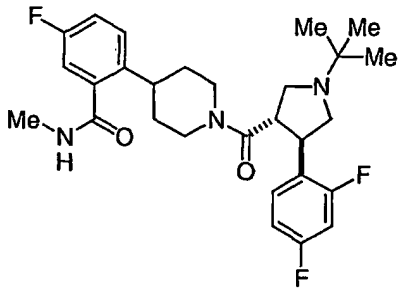
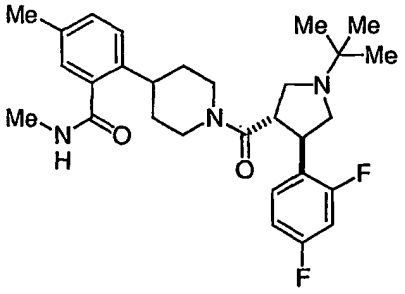
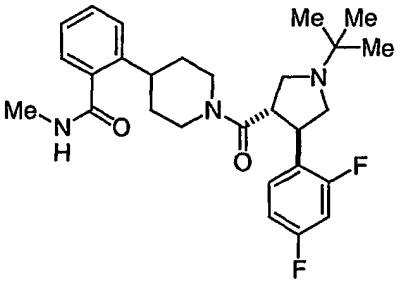
in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy; and wherein any methylene (CH_2) carbon atom in R^3 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl; or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group; and

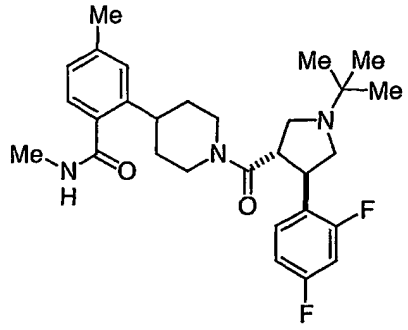
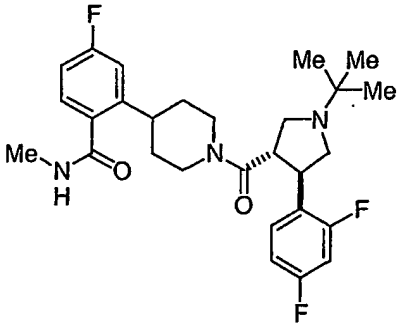
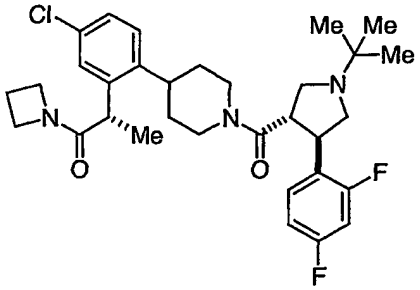
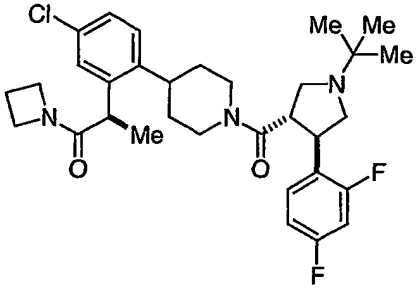
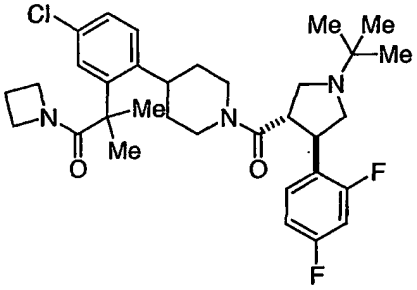
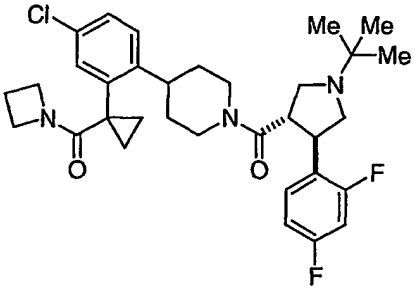
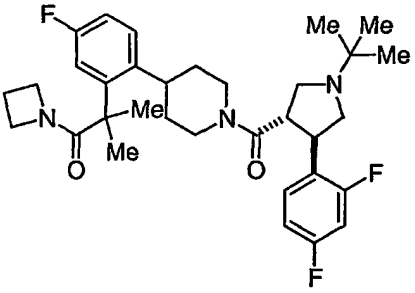
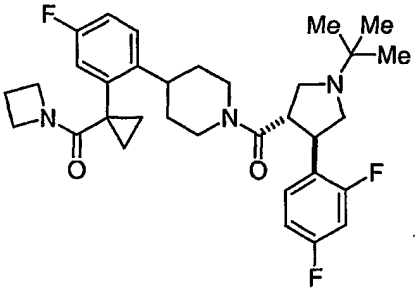
each R^4 is independently selected from the group consisting of

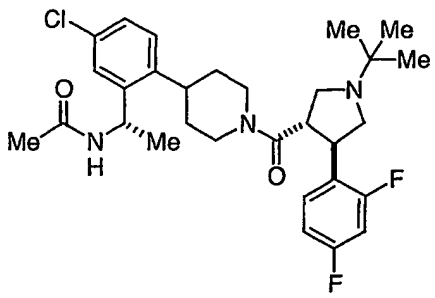
hydrogen,
C_{1-8} alkyl,
phenyl,
heteroaryl,
$(CH_2)_{0-1}$ heterocyclyl, and
C_{3-6} cycloalkyl;

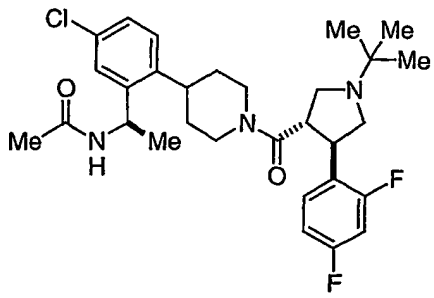
wherein alkyl, phenyl, heteroaryl, heterocyclyl, and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy; or two R^4 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC_{1-4} alkyl.

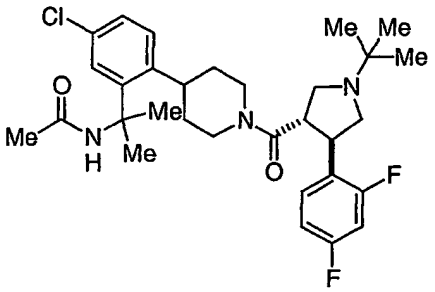
11. The compound of Claim 10 selected from the group consisting of:

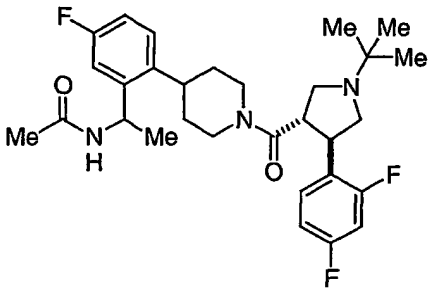





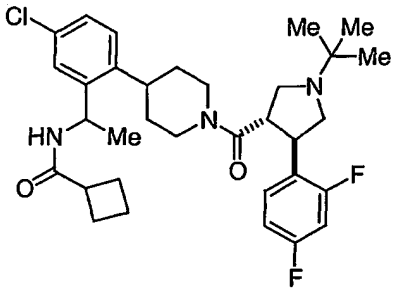









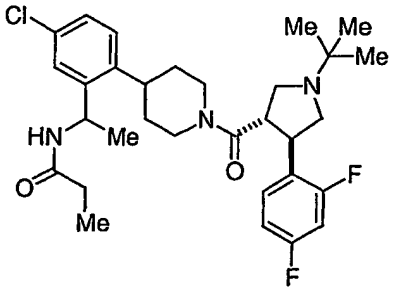


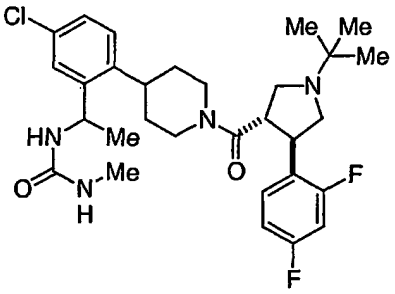


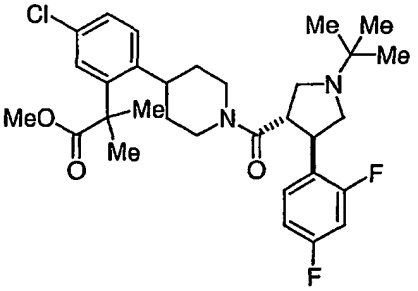


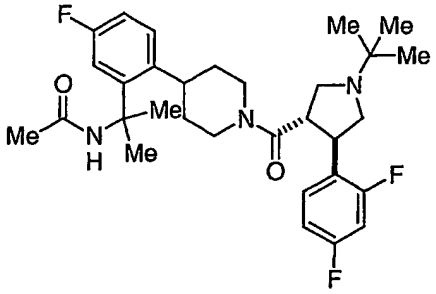


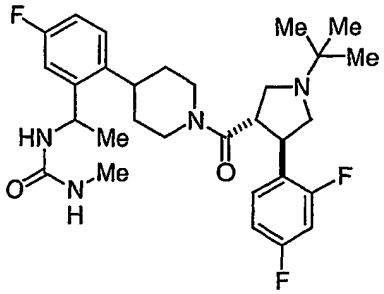


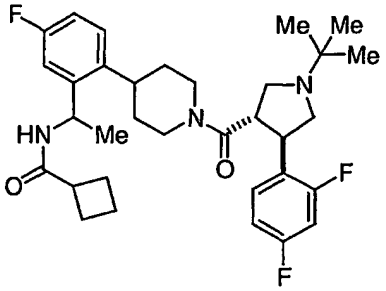


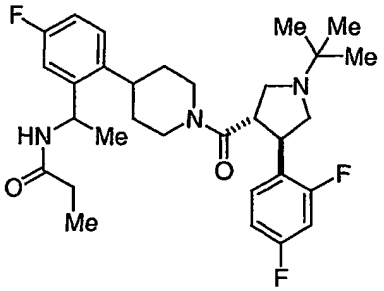


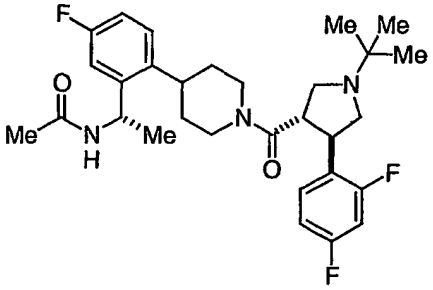


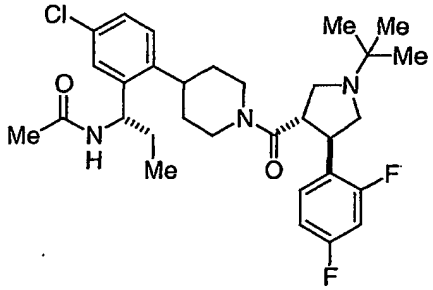




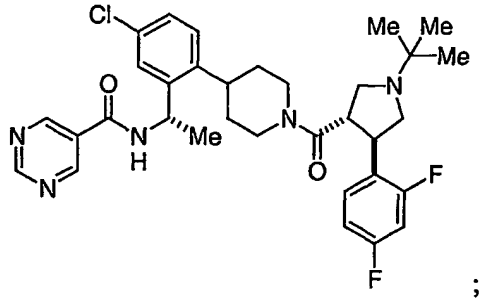








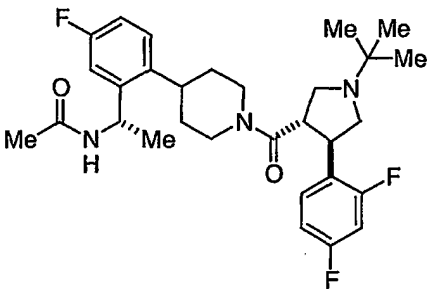
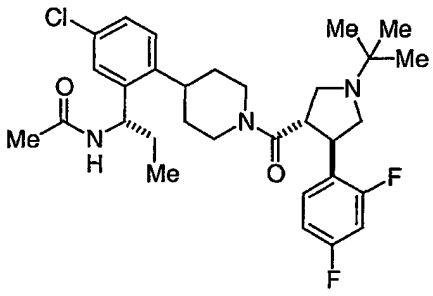
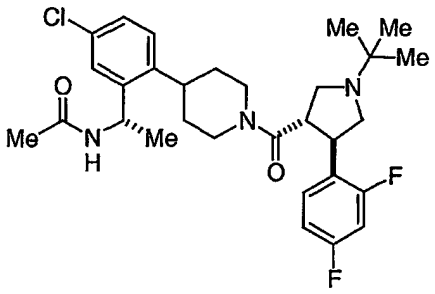
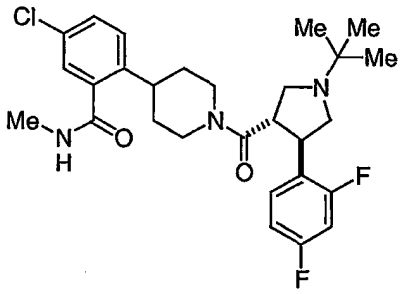
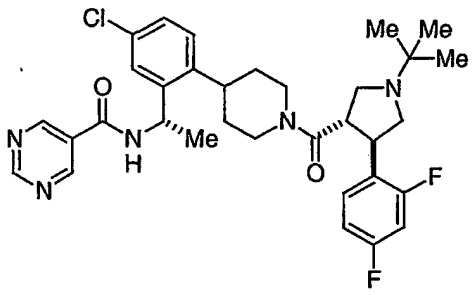
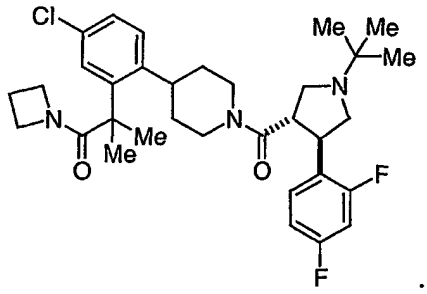
and



;

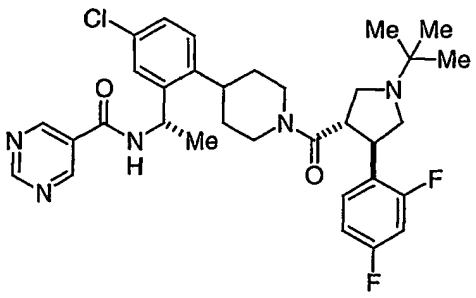
or a pharmaceutically acceptable salt thereof.

12. The compound of Claim 11 which is selected from the group consisting of:






and

;

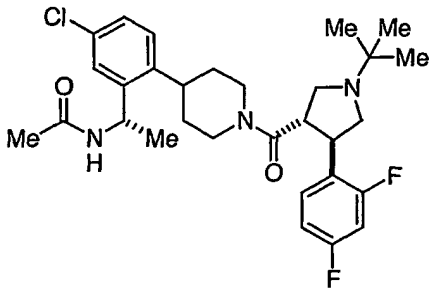
or a pharmaceutically acceptable salt thereof.

13. The compound of Claim 12 which is:



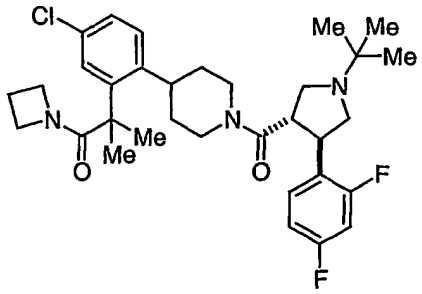
or a pharmaceutically acceptable salt thereof.

14. The compound of Claim 12 which is:



or a pharmaceutically acceptable salt thereof.

15. The compound of Claim 12 which is:



or a pharmaceutically aceptable salt thereof.

16. A method for the treatment or prevention of disorders, diseases or conditions responsive to the activation of the melanocortin-4 receptor in a mammal in need thereof which comprises administering to the mammal a therapeutically or prophylactically effective amount of a compound according to Claim 1.

17. A method for the treatment or prevention of obesity in a mammal in need thereof which comprises administering to the mammal a therapeutically or prophylactically effective amount of a compound according to Claim 1.

18. A method for the treatment or prevention of diabetes mellitus in a mammal in need thereof comprising administering to the mammal a therapeutically or prophylactically effective amount of a compound according to Claim 1.

19. A method for the treatment or prevention of male or female sexual dysfunction in a mammal in need thereof comprising administering to the mammal a therapeutically or prophylactically effective amount of a compound according to Claim 1.

20. A method for the treatment or prevention of erectile dysfunction in a mammal in need thereof comprising administering to the mammal a therapeutically or prophylactically effective amount of a compound according to Claim 1.

21. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier.

22. The pharmaceutical composition of Claim 21 further comprising a second active ingredient selected from the group consisting of an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α-glucosidase inhibitor, an HMG-CoA reductase inhibitor, an anti-obesity serotonergic agent, a β3 adrenoreceptor agonist, a neuropeptide Y1 or Y5 antagonist, a pancreatic lipase inhibitor, a melanin-concentrating hormone receptor antagonist, and a cannabinoid CB_1 receptor antagonist or inverse agonist.

23. The pharmaceutical composition of Claim 21 further comprising a second active ingredient selected from the group consisting of a type V cyclic-GMP-selective phosphodiesterase inhibitor, an α_2-adrenergic receptor antagonist, and a dopaminergic agent.

24. A method of treating erectile dysfunction in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of the composition of Claim 23.

25. A method of treating erectile dysfunction in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1 in combination with a type V cyclic-GMP-selective phosphodiesterase inhibitor, an α_2-adrenergic receptor antagonist, or a dopaminergic agent.

26. A method of treating diabetes or obesity in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1 in combination with an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α-glucosidase inhibitor, an HMG-CoA reductase inhibitor, an anti-obesity serotonergic agent, a β3 adrenoreceptor agonist, a neuropeptide Y1 or Y5 antagonist, a pancreatic lipase inhibitor, a melanin-concentrating hormone receptor antagonist, or a cannabinoid CB_1 receptor antagonist or inverse agonist.

27. A method of treating obesity in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of the composition of Claim 22.

28. The compound of Claim 12 wherein the pharmaceutically acceptable salt thereof is the hydrochloride salt.